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Cataract surgery and adjuvant treatments for patients with posterior chamber diseases

Cataract surgery and adjuvant treatments

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Abstract

Purpose of the study: Define recommendations and estimate the value of anti-VEGF therapy applied during cataract surgery or in perioperative period in patients with AMD or DR.

Procedures: A query was created and applied in PubMed. The found articles were then selected according to inclusion and exclusion criteria.

Results: All patients presented VA improvement after surgery. Patients undergoing adjuvant anti-VEGF injection when subject to cataract surgery, presented lower ME incidence in a group with preoperative NPDR without ME, statistically significant better VA with CMT decrease in a group with preoperative NPDR and ME and no increase of exudation after surgery in a group with preoperative wet AMD.

Conclusions: We recommend the use of bevacizumab as adjuvant treatment in patients with DR or wet AMD undergoing cataract surgery.

Message of the paper: Anti-VEGF plays an important role as an adjuvant treatment in cataract surgery.

Key words: “cataract surgery”, “age related macular degeneration”, “diabetic retinopathy” and “Anti-VEGF”

Introduction

Cataract extraction with intra-ocular lens implantation is a common procedure that in patients without retinal pathology is known to increase visual acuity (VA) and by that life quality.

Pathologies of the posterior chamber of the eye, such as age related macular degeneration (AMD) and diabetic retinopathy (DR), have high prevalence and often coexist in patients with cataracts. For that reason, it is common to see these patients being subject to cataract extraction, arising concerns whether surgery, even an uneventful one [1], could worsen retinal diseases, compromising visual acuity outcomes. Despite the existence of many studies addressing this subject, controversy remains whether these pathologies really worsen after surgery.

Some studies relating cataract surgery with DR reported increased risk of progression [2, 3] however others simply stated that this progression was the result from natural course of disease [3-9]. In a review summarizing recent prospective studies outcomes [3], authors concluded that there is an increased risk of worsening for patients with severe non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), as well as an increased risk of development and persistence of macular edema (ME) if present prior to surgery or in patients with severe NPDR. However, patients with diabetes but without DR, with mild-to-moderate NPDR or without ME prior to surgery showed no increased risk of progression or incidence of DR or ME.

In what concerns AMD progression after cataract extraction, all persists even more controversial. Some suggest a relation between cataract surgery and late AMD [10, 11], others found an association with early AMD [12] and others found no relation between surgery and progression of AMD [13]. Confusion factors such as coexistence of both diseases in elderly populations and presence of comorbidities (cardiovascular disease, hypertension) that may aggravate both diseases, persist until today making data interpretation more difficult. [14]. A recent review [15] about this question remain inconclusive but suggest that cataract surgery increases VA without an increased risk of progression to exudative AMD.

Nevertheless, it is known that patients undergoing cataract extraction are subject to an aggression that consequently causes inflammation by liberation of inflammatory mediators such as prostaglandins and vascular endothelial growth factor (VEGF). These mediators,

particularly VEGF, were shown to be increased in aqueous humour after cataract surgery [14] and in patients with PDR or wet AMD [15-18]. Consequently, VEGF may be a key mediator to aggravation of retinal pathologies after cataract extraction, acting mainly by increasing retinal vessel permeability [19]. In this context, it is important to assess whether in these patients anti-VEGF adjuvant treatments minimize retinal disease risk of progression and by that promote maximal visual acuity improvement.

There are three different anti-VEGF agents with different characteristics and costs (aflibercept, bevacizumab and ranibizumab) in ophthalmologic clinical practice. Some of them were developed with eye treatment in mind, while others were developed for a different purpose (metastatic cancers) and were then adapted to off-label intra-ocular use (bevacizumab). Despite that, all seem to have similar efficacy and safety in retinal pathologies management, however with discrepant prices [16]. Bevacizumab is significantly cheaper than the other two drugs. However, there are no studies comparing each of these agents as adjuvant drugs in cataract surgery, reason why there is no clear indication of each of them is the best in this context.

This article reviews the combination of cataract surgery with adjuvant intravitreal anti - VEGF injection in patients with DR and AMD.

Methods

The objective of this article is to define recommendations and estimate the value of anti VEGF therapy applied during cataract surgery or in perioperative period in patients with AMD or DR.

The following query was used in PubMed data base: ("Cataract Extraction"[Mesh] OR "Cataract Extraction"[All Fields] OR cataract surgery OR phacoemulsification surgery) AND (bevacizumab OR Ranibizumab OR aflibercept OR pegaptanib OR Avastin OR Lucentis OR Eylea OR Macugen OR anti-vascular endothelial growth factor OR anti-VEGF OR intraoperative Intravitreal injection).

The found articles were subject to inclusion and exclusion criteria, first in their titles and in case of doubts in their abstracts. After this selection, we searched the full text of the remaining articles using Endnote® (Version X7.2.1). The selected articles with full text accessibility were fully analyzed and used for writing this review.

Inclusion Criteria	**Exclusion Criteria**
Study includes patients with AMD or DR (a ny stage) undergoing cataract surgery and tr eated with anti-VEGF drugs during surgery or in perioperative period.	Study refers to patients without AMD or DR
	Study refers to other adjuvant treatments
	Single case report
	Study published over 10 years
	Study in other language than English or Portuguese

Results

After performing a search on PubMed, 175 articles were found. Of these, according to the methodology described above, 16 were included and 159 were excluded. The included articles were then divided according to pathology (diabetic retinopathy and age related macular degeneration) and fully read.

The studies regarding diabetic retinopathy were then further divided depending on grade of macular disease at the preoperative period. As result, three groups were created, dividing patients without macular edema (ME) (group 1), patients with ME (group 2) and patients with PDR or severe NPDR (group 3).

In group 1 we identified three prospective randomized studies that are summarized in table 1 [17-19]. In these studies, patients undergoing surgery with intraoperative injection (intervention group (IG)) show best corrected visual acuity (BCVA) improvement, however without significant difference compared with patients that did not receive intraoperative anti - VEGF injection (control group (CG)). Moreover, no differences in DR progression were also found between groups. Nevertheless, IG presented a decreased ME incidence as well as a central macular thickness (CMT) tendency to decrease. [17, 18]. Study [18] used bevacizumab and studies [17, 19] used ranibizumab in IG.

Group 2 included five studies divided into two prospective randomized studies, one prospective case series, one retrospective nonrandomized study and one case report. Detailed characteristics were summarized in table 2 [20-24]. Selected studies in this group presented significant improvement of visual acuity after surgery [1, 20-22, 24, 25]. However, significantly greater increase in visual acuity was seen in the IG [22-24] in which all patients were injected with bevacizumab. In what concerns central macular thickness (CMT), control groups show a significant increase when compared to preoperative values [22-24], and intervention groups present a significant decrease in CMT maintained for up to 3 months [1, 21, 22, 24].

In group 3 two prospective randomized studies were included and summarized in table 3 [26, 27]. These studies, including also patients with more severe conditions such as severe types of NPDR or PDR [26, 27] showed postoperative increase of BCVA and CMT during follow-up. Nevertheless, none of this changes presented statistically significant differences between IG (with both studies using bevacizumab) and CG [26, 27]. Despite that, patients

subject to anti VEGF injection show statistically significant lower progression of diabetic retinopathy and diabetic maculopathy.

In what concerns wet AMD, a total of six studies were included and summarized in table 4 [28-33]. From these, five were retrospective case series and one was an open label prospective study. In all studies all patients were treated with anti-VEGF. However, in three studies patients were injected during surgery for active exudation [30, 32, 33], while in the other three studies eyes were treated with anti-VEGF in a perioperative basis in order to obtain an exudation free phase before surgery [28, 29, 31]. On the other hand, some studies injected patients with either bevacizumab or ranibizumab [28, 30, 31] , others with bevacizumab [32, 33] and another with ranibizumab [29]. In terms of visual acuity, all studies show a statistically significant improvement during follow-up [14, 28-32]. Still, no VA significant difference was found between patients in exudation free phase before surgery and the ones receiving intraoperative anti-VEGF therapy for active choroidal neovascular complex leakage [30]. On the other hand, differences between frequency of anti-VEGF injections before and after surgery achieved no statistically significance in [29, 31]. Despite that, patients with longer exudation free period before surgery and longer time between exudative AMD diagnosis and surgery, presented smaller recurrence of exudation after surgery [28]. In what concerns CMT, patients in exudation free phase before surgery presented statistically significant increase of CMT one month after surgery [29] and patients injected during surgery shown CMT decrease [32].

Discussion

All the recommendations presented in the following discussion should be put in perspective as their applicability depends on the chosen anti-VEGF agent. In other words, there is a big financial difference between applying bevacizumab as an adjuvant agent, which would add around 50$ to the cost of surgery, or to use ranibizumab or aflibercept with each dose costing around 2000$ [16]. Recently, aflibercept has been pointed to achieve slightly better VA in patients with diabetic retinopathy with greater vision loss [34] as well as in patients with wet AMD that do not respond to other anti-VEGF drugs [35]. However, at least in patients with wet AMD, benefits were considered modest and not cost-efficient compared with bevacizumab [16].

Nevertheless, there are no studies comparing each of the anti-VEGF agents as adjuvant drugs in cataract surgery, reason why there is no clear indication of each of them is the best in this context. Also, there are no studies in which aflibercept was used peri-operatively or intra-operatively. Moreover, we found no differences between results presented by studies using bevacizumab or ranibizumab, supporting that it is reasonable to think that bevacizumab is a valid and cheap option for adjuvant therapy in cataract surgery, as it can achieve similar outcomes as other drugs.

Diabetic retinopathy and cataract surgery

Evidence presented by articles in group 1 support that patients with NPDR without ME might benefit from adjuvant treatment with anti-VEGF as it is a safe procedure that reduces macular edema incidence even though it does not reflect in greater BCVA improvement during 6 months follow-up. However, the lower ME incidence in IG may in a longer follow-up period translate into better VA outcomes considering the fact that macular edema is known to be the most important and common cause of central vision loss in diabetic patients [1]. Nevertheless, in study [19] in which patients with stable DR and with either no ME or mild ME were included, IG had statistically better BCVA at 6 months follow-up. However, the fact that patients with mild ME were included may be a cause of confusion and the reason why better BCVA improvement was seen in IG.

In group 2, patients with DR and ME were also shown to benefit from cataract extraction, especially when combined with intravitreal anti-VEGF injection which show consistently greater VA improvement, along with significant decrease in CMT and ME. Although these CMT measurements should not directly evaluate a visual outcome, anatomic improvement in diabetic ME is known to be highly correlated with functional improvement in visual acuity [24] as also shown by Takamura, Kubo [22] in which there was statistical correlation between BCVA and CMT in both groups. Even though there is no class A evidence of efficacy for intravitreal anti-VEGF injection, this option should be taken into account seriously in cases in which patients with DME have cataract surgery.

On the other hand, studies that included severe NPDR and PDR also contained patients with any other type of NPDR, reason why the results presented in group 3 reflect overall changes and not particularly patients with severe NPDR and PDR. For that reason, it is difficult to draw any conclusion whether this treatment should be performed in more advanced stages of DR. Nevertheless, there is at least theoretical benefit and it seems to be safe with no complications reported in these patients.

Wet AMD and cataract surgery

In what concerns patients with wet AMD, the combination of cataract extraction with adjuvant anti-VEGF agents appears to be beneficial and safe, as consistence VA gains were achieved without increased incidence of perioperative complications or macular adverse events. Moreover, frequency of injections is pointed to be the same before and after surgery, suggesting that phacoemulsification accompanied by operative or perioperative anti-VEGF injection does not increase exudation or change the characteristics of the underlying choroidal neovascularization. An exception to this statement was found in article [30] in which an intensive treatment and retreatment injection protocol ((PrONTO study protocol [36]) was implemented before surgery, resulting in a significantly lower injection frequency after surgery. However, this main difference with others studies can be justified by their intensive preoperative protocol which perhaps resulted in more patients in remission phase before surgery. On the other hand, it seems to be more beneficial to perform cataract extraction after longer exudation free periods in order to minimize exudation recurrence. However, specific guidelines are yet to be made. However, performing cataract surgery sooner may improve

patient visual acuity faster and increase quality of life in an elderly population. Questions whether this adjuvant therapy should be used during surgery or in a perioperative basis or even which are the benefits comparing with other patients not receiving this treatment remain unclear. These questions can only be answered with clinical trials.

Conclusion

Patients with NPDR with or without ME, benefit from anti-VEGF adjuvant treatment when subject to cataract surgery. However, evidence degree is higher for patients with ME in which an intraoperative anti-VEGF injection resulted in statistically significant better BCVA improvement.

Indications for more severe retinal status, including severe NPDR and PDR remain unclear, without studies objectively addressing the question whether these particular patients benefit from cataract extraction with anti-VEGF adjuvant treatment. However, it should not be forgotten that it is a safe procedure with at least theoretical benefit for these patients.

In what concerns patients with wet AMD, evidence lacks some support as no clinical trials were found, however, without reported complications it is fair to say that anti-VEGF treatments play an important role controlling exudation before and after surgery. For that reason, it is advisable to use this adjuvant treatment in wet AMD patients undergoing cataract surgery. Nevertheless, it is not clear which is the better approach. Whether promoting a more intensive treatment before surgery or injecting during surgery remains unanswered.

In conclusion, we recommend the use of intraoperative bevacizumab in patients with DR and the intraoperative or perioperative use of this drug, according to retinal exudation status, for patients with wet AMD undergoing cataract surgery.

Disclosure

The authors have no financial interest in any material or method mentioned in this study.

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Table 1 – Patients with DR and without ME

Study	Follow-up	Results		Complications
		Visual Acuity Outcomes	Other outcomes	
Udaondo, Garcia-Pous [17] – Prospective Randomized Study Patients: 54 eyes in 54 patients with cataract and mild to moderate NPDR without macular edema preoperatively Intervention group (IG): 27 eyes- intravitreal ranibizumab (0.5mL of solution at 10 mg/mL) at the end of phacoemulsification with IOL implantation Control group (CG): 27 eyes - phacoemulsification with IOL implantation	3 months: • slit lamp examination of the anterior and posterior segment • Visual acuity with and without correction • Central macular thickness by OCT • IOP measurements • Incidence of CSME Preoperatively, 1 and 3 months after surgery	• Visual acuity outcomes were not specified.	<u>Central macular thickness:</u> • Increased from baseline to month 1 (both groups) • Decreased from month 1 to month 3 (both groups) <u>Incidence of CSME:</u> • One month after surgery CG= 25.92% IG= 3.70% • Three months after surgery CG= 22.22% IG=3.70%	No complications were reported.
Fard, Yazdanei Abyane [18] - prospective randomized study Patients: cataract patients with preexisting moderate or severe NPDR without ME having phacoemulsification and intraocular lens (IOL) implantation Intervention group (IG): 31 eyes- received 1.25 mg of intravitreal bevacizumab at the end of phacoemulsification with IOL implantation	6 months: • Best corrected visual acuity • Central macular thickness • Rate of DR progression • Rate of laser therapy after surgery • Macular edema incidence • IOP measurements	• There was no statistically significant difference in postoperative visual acuity of both groups at 6 months (P=0.3).´	<u>Central Macular Thickness:</u> • 1 month after surgery: CG showed a significant increase (P=0.002) in CMT, whereas the IG did not show an increase. • 6 months after surgery: there was no significant difference in CMT between the two groups <u>Progression of DR (6months):</u> • CG:7 patients (23.3% of eyes) • IG: 5 patients (16.1% of eyes) (P=0.47, chi-square test) <u>Rate of laser therapy:</u>	No complications were reported.

Control group (CG): 30 eyes - phacoemulsification with IOL implantation	Preoperatively and 1 day, 4 weeks, 3- and 4-months after surgery		• There was no statistical difference between the 2 groups (P=0.67, chi-square test). <u>Macular edema incidence:</u> • Lower incidence in IG at month 3 • No differences in incidence between groups at month 6 • No patients developed CSME. <u>IOP:</u> • There was no significant increase in intraocular pressure at 1 and 6 months after surgery in either group.	
Chae, Joe [19] – Prospective randomized study Patients: 80 eyes of 80 patients with significant cataract and NPDR with no or mild ME, underwent phacoemulsification and intraocular lens implantation Intervention group (IG): 40 patients- intravitreal ranibizumab injection (0,05 ml of solution containing 0,5 mg of ranibizumab) combined with phacoemulsification and IOL implantation Control group (CG): 40 patients – phacoemulsification with IOL implantation	6 months: • Best corrected visual acuities • Central subfield thickness • Total macular volume • ME occurrence (meaningful ME when CST increase 0.60 relative to baseline) Baseline, 1 week, 1-, 3-, 6-months	• No differences between groups at baseline, 1 week, 1- and 3- month follow up visits • Greater BCVA improvement in IG at 6 month follow up visit (P=0.046)	<u>Central Subfield Thickness relative to baseline</u>: • Significantly lower in IG group at 1 week and 1 month • No differences between groups at 3- and 6-months <u>Total Macular Volume relative to baseline</u>: • Increased in both groups • IG exhibited smaller change in TMV at all follow ups • The difference between the 2 groups was most significant at the 1-week follow-up visit (P < 0.001) but remained significant at the 6-month visit (P = 0.017) <u>ME Occurrence Rate (calculated by CST):</u> • Significantly lower rate in IG at 1 month • No statistical differences at 3- and 6- months <u>Comparison of Fluorescein Angiography Grading at 3- and 6- months:</u> • No statistical differences between groups	Two adverse events: • IG: one vitreous hemorrhage • CG: one vitreous hemorrhage

Table 2 - Patients with DR and ME

Study	Follow-up	Results		Complications
		Visual Acuity Outcomes	Other outcomes	
Wahab and Ahmed [20] - prospective case series Patients: 38 patients with clinically significant macular edema, hypertension and diabetes (type II) were subjected to phacoemulsification and IOL implantation. All the patients had prior macular grid treatment and intra-operative injection of intra-vitreal Bevacizumab (Avastin)	6 months: • Best corrected visual acuity Preoperatively and 1 day, 1 week, and 1, 2, 3, and 6 months after surgery	<u>Best corrected distant visual acuity of (6 months follow up)</u>: • 6/6 to 6/9 in 23(60.5 %) • 6/12 in 11(28.9%) • 6/24 in 4(10.5%) <u>Best corrected near acuity of (6 months follow up)</u>: • N/6 in 22(57.8%) • N/8 in 12(31.4%) • N/12 in 4(10.5%)	Not studied.	No complications were reported.
Akinci, Batman [21] - case reports Patients: 31 patients with diabetes with CSME and cataract interfering with macular laser photocoagulation, who have undergone phacoemulsification with intravitreal injection of 1.25 mg bevacizumab. All eyes had undergone macular focal or modified grid laser photocoagulation 1 month after the surgery.	3 months: • Best corrected visual acuity • Central macular thickness • IOP measurements Preoperatively and 1 day, 5 days, 1 month, and 3 months after the surgery.	• The BCVA level recorded at the first and third months after the surgery were significantly higher than the initial BCVA ($P = 0.004$) • BCVA increased in all eyes and ≥2 Snellen lines gain in BCVA was achieved in 26 eyes.	<u>Central Macular Thickness:</u> • CMT recorded at the first and third months after the surgery were significantly lower than the initial CMT ($P < 0.001$, $P < 0.001$). • Central macular thickness decreased in all eyes. <u>IOP:</u> • Postoperative IOP transient elevation was observed in 4 patients	No complications were reported.
Takamura, Kubo [22] - Prospective, randomized, double masked cohort study.	3 months: • Best corrected visual acuity	• Both groups had significant BCVA improvements.	<u>Retinal thickness:</u> • 1 and 3 months after surgery: CG: RT increased significantly	No complications were reported.

Patients: 42 eyes with diabetic macular edema (DME) of 42 patients with type 2 diabetes mellitus. Patients with PDR were excluded. Intervention group (IG): 21 eyes - received 1.25 mg of intravitreal bevacizumab at the end of phacoemulsification with IOL implantation Control group (CG): 21 eyes - phacoemulsification with IOL implantation	• Retinal thickness Preoperatively (1 day before surgery), 1 – and 3 – months after surgery	• VA in the bevacizumab group was significantly better at month 3 than in control group (P =0.034) • Improvement of BCVA (>3 line): IG: 15 eyes (71.4%) CG: 8 eyes (38.1%)	IG: RT decreased significantly • 3 months after surgery visual acuity and central RT were significantly correlated (ordinary least-squares regression analysis) in both the control group (P = 0.0001) and the bevacizumab group (P = 0.014)	
Lanzagorta-Aresti, Palacios-Pozo [23] - Prospective Randomized Study Patients: 26 type II diabetic patients with NPDR and diffuse macular edema undergoing cataract surgery Intervention group (IG): 13 eyes - received intravitreal bevacizumab at the end of phacoemulsification with IOL implantation Control group (CG): 13 eyes- received intravitreal with balanced salt solution at the end of phacoemulsification with IOL implantation	6 months: • Best-corrected visual acuity • Central macular thickness Preoperatively, 3 and 6 months after surgery	<u>Best-corrected visual acuity at 3 and 6 Months:</u> • CG: no significant differences at month 3, with P= 0.528; visual acuity significant loss at month 6 (P=0.008) • IG: improved significantly at month 3 and 6 (P=0.048; P=0.035) • There was statistically differences between both groups at month 3 and 6 (P=0.036; P=0.046)	<u>Central macular thickness:</u> • CG: significantly increased (P=0.001) • IG: no increase was observed There was statistically differences between both groups at month 3 and 6 (P=0.046; P=0.004)	No complications were reported.

Chen, Liu [24] – retrospective nonrandomized study Patients: 29 eyes of 28 diabetic patients with cataract and CSME. Patients with PDR were excluded. Intervention group (IG): 15 eyes - received intravitreal 2.5-mg bevacizumab at the end of phacoemulsification with IOL implantation Control group (CG): 14 eyes- phacoemulsification with IOL implantation	3 months: • Best-corrected visual acuity • Central macular thickness • IOP measurements Preoperatively, day 1, 1-, 4-, 8-, and 12 weeks, 3 months after surgery.	• CG: improved insignifi cantly at week 1 and 4 (P>0.05) and significantly at week 8 and 12. • IG: improved significantly at 1, 4, 8, and 12 weeks after surgery (P < 0.05)	<u>Central macular thickness:</u> • CG: increased from baseline to week 4 and then decreased (P>0.05) • IG: decreased significantly at 4, 8, and 12 weeks after surgery (P<0.05) <u>IOP:</u> • There was no increase in IOP	No complications were reported.

Table 3 - Patients with severe NPDR or PDR

Study	Follow-up	Results		Complications
		Visual Acuity Outcomes	Other outcomes	
Salehi, Beni [26] - Prospective Randomized Study Patients: 57 eyes of 57 patients diagnosed with any type of NPDR or PDR, CSME and concurrent significant cataract Intervention group (IG): 27 eyes- 1.25mg intravitreal bevacizumab at the end of phacoemulsification with IOL implantation Control group (CG): 30 eyes- phacoemulsification with IOL implantation	6 months: • Best corrected visual acuity • Central macular thickness by OCT • Progression of DR and diabetic maculopathy • Postoperative laser therapy • Progression to neovascular glaucoma (NVG)	• 1 month after surgery: Both groups had statistically significant improvement of BCVA • 6 months after surgery: no statistically significant difference in postoperative visual acuity between the 2 groups	<u>Central Macular Thickness:</u> • there was no significant difference between both groups concerning CMT at baseline and 6 months <u>Progression of Diabetic Retinopathy:</u> • CG: 40% • IG: 11% (P<0,005) <u>Progression of diabetic maculopathy:</u> • CG: 15 eyes (50%) • IG: 2 eyes (7.4%) (P =0.0008) <u>Postoperative laser therapy</u>: • there was no statistical difference in the rate of laser therapy between groups. (laser therapy was used in – CSME and PDR) <u>Progression to NVG during the follow-up:</u> • CG: 5 eye (13%) • IG: 1 eye (3%)	No complications were reported
Cheema, Al-Mubarak [27] - prospective randomized study Patients: 68 eyes (68 patients) with DM and diabetic retinopathy (NPDR or PDR and CSME) undergoing cataract surgery and IOL implantation Intervention group (IG): 35 eyes- received 1.25 mg of	6 months: • progression of DR and diabetic maculopathy • Best-corrected visual acuity • central macular thickness • postoperative laser therapy	• Improved in both groups. • There was no statistically significant difference in postoperative visual acuity at any time point between both groups.	<u>Central macular thickness:</u> • increased in both groups • difference between groups was not statistically significant at any time <u>Progression of DR</u>: • CG: 45.45% • IG: 11.42% Difference between both groups was statistically significant (P=0.002)	No complications were reported.

intravitreal bevacizumab at the end of phacoemulsification with IOL implantation Control group (CG): 33 eyes - phacoemulsification with IOL implantation	• progression to neovascular glaucoma (NVG) Preoperatively, 1 day, 1, 2, and 4 weeks, 2, 3, 4, 5, and 6 months.		<u>Progression of DM:</u> • CG: 51.51% • IG: 5.71% Difference between both groups was statistically significant (P=0.001) <u>Laser photocoagulation was performed in</u>: • CG: 48.48% • IG: 57.14% Difference between both groups was not statistically significant (P=0.475) <u>Postoperative progression to NVG</u>: • CG: 2 eyes • IG: 0 eyes	

Table 4 – Patients with wet AMD

Study	Follow-up	Results		Complications
		Visual Acuity Outcomes	Other outcomes	
Lee, Kim [28] - retrospective, observational case series Patients: 39 eyes of 39 patients who underwent cataract surgery and had been previously treated with anti-VEGF (bevacizumab or ranibizumab) for exudative AMD.	6 months: • Visual acuity • Exudative AMD recurrence • Time between exudative AMD diagnosis and surgery • Exudation-free period before surgery Preoperatively, 1- and 6-months after surgery	BCVA: • significantly improved 1 and 6 months after surgery	<u>Time between exudative AMD diagnosis and surgery:</u> • Recurrence group: 13.3±10.1 • No recurrence group: 27.9±16.6 • Statistically significant difference between groups (P= 0,001) <u>Exudation-free period before surgery:</u> • Recurrence group: 6.5±5.4 • No recurrence group: 15.2±10.2 • Statistically significant difference between groups (P< 0,001)	No complications were reported.
Grixti, Papavasileiou [29] - Retrospective, noncomparative, and interventional case series Patients: 30 eyes from 29 subjects with neovascular AMD treated with intravitreal anti - VEGF injections (ranibizumab) who underwent phacoemulsification after achieving an exudation free phase of at least 3 months.	6 months: • BCVA • Central macular thickness • Frequency of anti-VEGF therapy Preoperatively; 1 month, 3 months, and 6 months postoperatively	BCVA: • Significant improvement at 3- and 6-months follow up	<u>Central macular thickness:</u> • increase between preoperative measurement and 1 month follow up (P=0.0093) • return to baseline at 3 months postoperatively (P=0.3811) <u>Frequency of anti-VEGF injections:</u> • no difference between the immediate 6 months before and after phacoemulsification	No complications were reported.
Tabandeh, Chaudhry [30] – Case series Patients: 30 eyes of 28 patients with occult or classic neovascular AMD treated by anti-VEGF (bevacizumab or ranibizumab) therapy before	6 months: • BCVA • Frequency of anti – VEGF therapy Preoperatively, 2 and 6 months after surgery**.**	BCVA: • Statistically significant improvement at all postoperative time points compared to baseline • No significant difference in visual	<u>Frequency of anti – VEGF therapy:</u> • Before surgery: 0,49 injections per month • After surgery: 0,32 injections per month • Statistically significant difference (P=0,002)	No perioperative complications or macular adverse events were reported.

cataract surgery. Some patients (8) received also an intraoperative injection.		improvement between patients in a exudation free phase before surgery and those who were receiving anti – VEGF therapy for active choroidal neovascular complex leakage		
Muzyka-Wozniak [31] - retrospective noncomparative interventional case-series study Patients: 16 eyes of 16 patients with choroidal neovascular AMD treated with anti – VEGF injections (bevacizumab or ranibizumab), undergoing phacoemulsification.	14 months: • BCVA • Median time interval between injections Baseline (before first injection), immediately before surgery, 1 month after surgery, endpoint (median 14 months)	BCVA: • Improved significantly after phacoemulsification and remained stable during follow-up	<u>Median time interval between injections:</u> • There was no statistically significant difference before and after phacoemulsification	
Furino, Ferrara [32] – open label prospective study Patients: 20 eyes of 20 patients with subfoveal neovascularization due to AMD and cataract had phacoemulsification, IOL implantation and 1,25 mg intravitreal injection of bevacizumab	1 month: • CDVA • Central retinal thickness • IOP Baseline and 1 month after surgery	CDVA: • Statistically significant improvement	<u>Central retinal thickness:</u> • Statistically significant reduction • No patient had an increase in central foveal thickness <u>IOP</u>: • did not change significantly	No complications were reported
Jonas, Spandau [33] – interventional case series study Patients: 11 eyes of 11 patients with exudative AMD (10 eyes) or exudative myopic macular				No complications were reported

degeneration (1 eye) underwent phacoemulsification and intravitreal injection of 1.5mg bevacizumab				

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